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(30) 1997/10/16 (08/951,733) US
(54) **GENES CODANT DES PROTEINES DE TELOMERASE**
(54) **GENES ENCODING TELOMERASE PROTEINS**

(57) L'invention concerne des molécules d'acide nucléique, qui codent des polypeptides du complexe télomérase. L'invention se rapporte également à des procédés de préparation desdites molécules d'acide nucléique et desdits polypeptides et à des procédés d'utilisation desdites molécules.

(57) Disclosed are nucleic acid molecules encoding polypeptides of the telomerase complex. Also disclosed are methods of preparing the nucleic acid molecules and polypeptides, and methods of using these molecules.

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(21) International Application Number: PCT/US97/21248 (22) International Filing Date: 13 November 1997 (13.11.97) (30) Priority Data: 08/871,189 15 November 1996 (15.11.96) US 08/873,039 11 June 1997 (11.06.97) US 08/951,733 16 October 1997 (16.10.97) US (71) Applicants: AMGEN INC. [US/US]; Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US). AMGEN CANADA INC. [CA/CA]; Suite 303, 6733 Mississauga Road, Mississauga, Ontario L5N 6J5 (CA). (72) Inventors: HARRINGTON, Lea, A.; 55 Pears Avenue, Toronto, Ontario M5R 1S9 (CA). ROBINSON, Murray, O.; 22623 Pacific Coast Highway, Malibu, CA 90265 (US). (74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BF, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GF, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NC, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GF, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NI, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>With amended claims and statement.</i> Date of publication of the amended claims and statement: 30 July 1998 (30.07.98)	

(54) Title: GENES ENCODING TELOMERASE PROTEINS**(57) Abstract**

Disclosed are nucleic acid molecules encoding polypeptides of the telomerase complex. Also disclosed are methods of preparing the nucleic acid molecules and polypeptides, and methods of using these molecules.

AMENDED CLAIMS

[received by the International Bureau on 19 June 1998 (19.06.98);
new claims 33-56 added; remaining claims unchanged (7 pages)]

1. A TP2 nucleic acid molecule encoding a polypeptide selected from the group consisting of:

5 (a) the nucleic acid molecule of SEQ ID NO:13;

(b) the nucleic acid molecule that is nucleotides 1920-2820 of SEQ ID NO:13;

(c) the nucleic acid molecule of SEQ ID NO:19.

10 (d) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:14, or a biologically active fragment thereof;

(e) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:20, or a biologically active
15 fragment thereof;

(f) a nucleic acid molecule that encodes a polypeptide that is at least 90 percent identical to the polypeptide of SEQ ID NO:14;

20 (g) a nucleic acid molecule that encodes a polypeptide that is at least 90 percent identical to the polypeptide of SEQ ID NO:20;

(h) a nucleic acid molecule that hybridizes under stringent conditions to any of (a)-(g) above; and

25 (i) a nucleic acid molecule that is the complement of any of (a)-(g) above.

2. The nucleic acid molecule that is SEQ ID NO:13 or SEQ ID NO:19.

30 3. The nucleic acid molecule that is nucleotides 1920-2820 of SEQ ID NO:13.

4. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:14 of SEQ ID NO:20.

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5. A nucleic acid molecule selected from the group consisting of: nucleotides 1-1689 of SEQ ID NO:13, nucleotides 1-1920 of SEQ ID NO:13, nucleotides 1920-2820 of SEQ ID NO:13, nucleotides 2089-2820 of SEQ ID NO:13, and nucleotides 2089-2859 of SEQ ID NO:13.

6. A nucleic acid molecule encoding amino acids 640-940 of the polypeptide of SEQ ID NO:14.

10 7. A vector comprising the nucleic acid molecule of claim 1.

8. A vector comprising the nucleic acid molecule of claim 2.

15

9. A vector comprising the nucleic acid molecule of claim 3.

20 10. A vector comprising the nucleic acid molecule of claim 4.

11. A vector comprising the nucleic acid molecule of claim 5.

25 12. A vector comprising the nucleic acid molecule of claim 6.

13. A host cell comprising the vector of claim 7.

30

14. A host cell comprising the vector of claim 8.

35 15. A host cell comprising the vector of claim 9.

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16. A host cell comprising the vector of claim 10.

5 17. A host cell comprising the vector of claim 11.

18. A host cell comprising the vector of claim 12.

10

19. A process for producing a TP2 polypeptide comprising the steps of:

(a) expressing a polypeptide encoded by the nucleic acid of claim 1 in a suitable host; and

15

(b) isolating the polypeptide.

20. The process of claim 19 wherein the polypeptide is SEQ ID NO:14 or SEQ ID NO:20.

20

21. The process of claim 19 wherein the polypeptide is amino acids 640-940 of SEQ ID NO:14.

22. A TP2 polypeptide selected from the group consisting of:

25

(a) the polypeptide of SEQ ID NO:14;

(b) the polypeptide that is amino acids 640-940 of SEQ ID NO:14;

(c) the polypeptide of SEQ ID NO:20; and

(d) a polypeptide that is at least 90 percent identical to any of the polypeptides of (a)-(c).

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23. A TP2 polypeptide that is the polypeptide of SEQ ID NO:14, SEQ ID NO:20, or a biologically active fragment thereof.

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24. A TP2 polypeptide selected from the group consisting of: amino acids 1-563 of SEQ ID NO:14; amino acids 1-640 of SEQ ID NO:14; amino acids 640-940 of SEQ ID NO:14; amino acids 696-940 of SEQ ID NO:14; and
5 amino acids 696-953 of SEQ ID NO:14.

25. The TP2 polypeptide of claim 22 that does not possess an amino terminal methionine.

10 26. A method of increasing proliferation of a cell, comprising expressing a nucleic acid encoding TP2 or a biologically active fragment thereof, in the cell.

15 27. A method of increasing telomerase activity in a cell, comprising expressing a TP2 gene, or a biologically active fragment thereof, in the cell.

20 28. A method of decreasing telomerase in a cell, comprising expressing a TP2 mutant in a cell, wherein the mutant does not have TP2 biological activity.

25 29. A nucleic acid molecule encoding a mutant TP2 polypeptide, wherein the codon for aspartic acid at amino acid position 868 or 869 is changed to a codon for alanine.

30 30. A nucleic acid molecule encoding a mutant TP2 polypeptide, wherein the codons for aspartic acid at amino acid positions 868 and 869 are changed to codons for alanine.

35 31. A polypeptide encoded by the nucleic acid molecule of claim 29.

32. A polypeptide encoded by the nucleic acid molecule of claim 30.

5 33. A TRIP1 nucleic acid molecule encoding a polypeptide selected from the group consisting of:
(a) the nucleic acid molecule of SEQ ID NO:1;
(b) the nucleic acid molecule of SEQ ID NO:2;
(c) a nucleic acid molecule encoding the
10 polypeptide of SEQ ID NO:3, SEQ ID NO:4, or a biologically active fragment thereof;
(d) a nucleic acid molecule that encodes a polypeptide that is at least 70 percent identical to the polypeptide of SEQ ID NO:3 or SEQ ID NO:4;
15 (e) a nucleic acid molecule that hybridizes under stringent conditions to any of (a)-(d) above; and
(f) a nucleic acid molecule that is the complement of any of (a)-(e) above.

20 34. The nucleic acid molecule that is SEQ ID NO:1.

35. The nucleic acid molecule that is SEQ ID NO:2.

25 36. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:3.

37. A nucleic acid molecule encoding the
30 polypeptide of SEQ ID NO:4.

38. A nucleic acid molecule encoding amino acids 1-871 of the polypeptide of SEQ ID NO:3.

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39. A vector comprising the nucleic acid molecule of claim 33.

40. A vector comprising the nucleic acid molecule of claim 34.

41. A vector comprising the nucleic acid molecule of claim 35.

42. A vector comprising the nucleic acid molecule of claim 36.

43. A vector comprising the nucleic acid molecule of claim 37.

44. A vector comprising the nucleic acid molecule of claim 38.

45. A host cell comprising the vector of claim 39.

46. A host cell comprising the vector of claim 40.

47. A host cell comprising the vector of claim 41.

48. A host cell comprising the vector of claim 42.

49. A host cell comprising the vector of claim 43.

50. A host cell comprising the vector of claim 44.

51. A process for producing a TRIP1 polypeptide comprising the steps of:

- 5 (a) expressing a polypeptide encoded by the nucleic acid of claim 1 in a suitable host; and
(b) isolating the polypeptide.

52. The process of claim 51 wherein the polypeptide is SEQ ID NO:3.

10

53. The process of claim 51 wherein the polypeptide amino acids 1-871 of SEQ ID NO:3.

54. A TRIP1 polypeptide selected from the group consisting of:

- 15 (a) the polypeptide of SEQ ID NO:3;
(b) the polypeptide that is amino acids 1-871 of SEQ ID NO:3; and
(c) a polypeptide that is at least 70 percent
20 identical to the polypeptide of (a) or (b).

55. A TRIP1 polypeptide that is the polypeptide of SEQ ID NO:3 or a biologically active fragment thereof.

25

56. The TRIP1 polypeptide of claim 52 that does not possess an amino terminal methionine.

STATEMENT UNDER ARTICLE 19

The claims of International Application WO 98/21248, published 22 May 1998, have been amended. Original claims 1 through 32 have not been amended, however, new claims 33 through 56 have been added. Claims 33 through 56 are directed to an aspect of the invention not originally claimed by Applicants. Specifically, claims 33 through 56 encompass telomerase protein 1 and DNA encoding therefor. Such claims are fully supported by the written description and the drawings.

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FIG.1A

ATGGAAAACTCCATGGGCATGTGTCTGCCCATCCAGACATCCTCTCCT
TGGAGAACCGGTGCCTGGCTATGCTCCCTGACTTACAGCCCTTGGAGAA
ACTACATCAGCATGTATCTACCCACTCAGATATCCTCTCCTTGAAGAAC
CAGTGCCTAGCCACGCTTCCTGACCTGAAGACCATGGAAAAACCACATG
GATATGTGTCTGCCCACCCAGACATCCTCTCCTTGGAGAACCAGTGCCT
GGCCACACTTTCTGACCTGAAGACCATGGAGAAACCACATGGACATGTT
TCTGCCCACCCAGACATCCTCTCCTTGGAGAACCGGTGCCTGGCCACCC
TCCCTAGTCTAAAGAGCACTGTGTCTGCCAGCCCCTTGTTCCAGAGTCT
ACAGATATCTCACATGACGCAAGCTGATTTGTACCGTGTGAACAACAGC
AATTGCCTGCTCTCTGAGCCTCCAAGTTGGAGGGCTCAGCATTTCTCTA
AGGGACTAGACCTTTCAACCTGCCCTATAGCCCTGAAATCCATCTCTGC
CACAGAGACAGCTCAGGAAGCAACTTTGGGTCGTTGGTTTGATTTCAGAA
GAGAAGAAAGGGGCAGAGACCCAAATGCCTTCTTATAGTCTGAGCTTGG
GAGAGGAGGAGGAGGTGGAGGATCTGGCCGTGAAGCTCACCTCTGGAGA
CTCTGAATCTCATCCAGAGCCTACTGACCATGTCCTTCAGGAAAAGAAG
ATGGCTCTACTGAGCTTGCTGTGCTCTACTCTGGTCTCAGAAGTAAACA
TGAACAATACATCTGACCCCAACCCTGGCTGCCATTTTTGAAATCTGTCTG
TGAACCTGCCCTCCTGGAGCCTGAGTTTATCCTCAAGGCATCTTTGTAT
GCCAGGCAGCAGCTGAACGTCCGGAATGTGGCCAATAACATCTTGGCCA

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FIG. 1B

TTGCTGCTTTCTTGCCGGCGTGTGCCCCACCTGCGACGATATTTCTG
TGCCATGTCCAGCTGCCTTCTGACTGGATCCAGGTGGCTGAGCTTTAC
CAGAGCCTGGCTGAGGGAGATAAGAATAAGCTGGTGCCCCCTGCCCCGCCT
GTCTCCGTACTGCCATGACGGACAAATTTGCCCAGTTTGACGAGTACCA
GCTGGCTAAGTACAACCCTCGGAAGCACCGGGCCAAGAGACACCCCCGC
CGGCCACCCCGCTCTCCAGGGATGGAGCCTCCATTTTCTCACAGATGTT
TTCCAAGGTACATAGGGTTTCTCAGAGAAGAGCAGAGAAAGTTTGAGAA
GGCCGGTGATACAGTGTCAGAGAAAAAGAATCCTCCAAGGTTACCCCTG
AAGAAGCTGGTTTCAGCGACTGCACATCCACAAGCCTGCCCAGCACGTTC
AAGCCCTGCTGGGTTACAGATACCCCTCCAACCTACAGCTCTTTTCTCG
AAGTCGCCTTCCTGGGCCTTGGGATTCTAGCAGAGCTGGGAAGAGGATG
AAGCTGTCTAGGCCAGAGACCTGGGAGCGGGAGCTGAGCCTACGGGGGA
ACAAAGCGTCGGTCTGGGAGGAACTCATTGAAAATGGGAAGCTTCCCTT
CATGGCCATGCTTCGGAACCTGTGCAACCTGCTGCGGGTTGGAATCAGT
TCCCGCCACCATGAGCTCATTCTCCAGAGACTCCAGCATGGGAAGTCGG
TGATCCACAGTCGGCAGTTTCCATTTCAGATTTCTTAACGCCCATGATGC
CATTGATGCCCTCGAGGCTCAACTCAGAAATCAAGCATTGCCCTTTCCT
TCGAATATAACACTGATGAGGCGGATACTAACTAGAAATGAAAAGAACC
GTCCCAGGCGGAGGTTTCTTTGCCACCTAAGCCGTCAGCAGCTTCGTAT

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FIG.1C

GGCAATGAGGATACCTGTGTTGTATGAGCAGCTCAAGAGGGAGAAGCTG
AGAGTACACAAGGCCAGACAGTGGAAATATGATGGTGAGATGCTGAACA
GGTACCGACAGGCCCTAGAGACAGCTGTGAACCTCTCTGTGAAGCACAG
CCTGCCCCCTGCTGCCAGGCCGCACTGTCTTGGTCTATCTGACAGATGCT
AATGCAGACAGGCTCTGTCCAAAGAGCAACCCACAAGGGCCCCCGCTGA
ACTATGCACTGCTGTTGATTGGGATGATGATCACGAGGGCGGAGCAGGT
GGACGTCGTGCTGTGTGGAGGTGACACTCTGAAGACTGCAGTGCTTAAG
GCAGAAGAAGGCATCCTGAAGACTGCCATCAAGCTCCAGGCTCAAGTCC
AGGAGTTTGATGAAAATGATGGATGGTCCCTGAATACTTTTGGGAAATA
CCTGCTGTCTCTGGCTGGCCAAAGGGTTCCTGTGGACAGGGTCATCCTC
CTTGGCCAAAGCATGGATGATGGAATGATAAATGTGGCCAAACAGCTTT
ACTGGCAGCGTGTGAATTCCAAGTGCCTCTTTGTTGGTATCCTCCTAAG
AAGGGTACAATACCTGTCAACAGATTTGAATCCCAATGATGTGACTC
TCAGGCTGTACTGATGCGATACTGAAGTTCATTGCAGAGCATGGGGCCT
CCCATCTTCTGGAACATGTGGGCCAAATGGACAAAATATTCAAGATTCC
ACCACCCCCAGGAAAGACAGGGGTCCAGTCTCTCCGGCCACTGGAAGAG
GACACTCCAAGCCCCTTGGCTCCTGTTTCCCAGCAAGGATGGCGCAGCA
TCCGGCTTTTCATTTTCATCCACTTTCCGAGACATGCACGGGGAGCGGGA
CCTGCTGCTGAGGTCTGTGCTGCCAGCACTGCAGGCCCCGAGCGGCCCT

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FIG. 1D

CACCGTATCAGCCTTCACGGAATCGACCTCCGCTGGGGCGTCACTGAGG
AGGAGACCCGTAGGAACAGACAACTGGAAGTGTGCCTTGGGGAGGTGGA
GAACGCACAGCTGTTTGTGGGGATTCTGGGCTCCCGTTATGGATACATT
CCCCCAGCTACAACCTTCCTGACCATCCACACTTCCACTGGGCCCAGC
AGTACCCTTCAGGGCGCTCTGTGACAGAGATGGAGGTGATGCAGTTCCT
GAACCGGAACCAACGTCTGCAGCCCTCTGCCCAAGCTCTCATCTACTTC
CGGGATTCCAGCTTCCTCAGCTCTGTGCCAGATGCCTGGAAATCTGACT
TTGTTTCTGAGTCTGAAGAGGCCGCATGTCGGATCTCAGAACTGAAGAG
CTACCTAAGCAGACAGAAAGGGATAACCTGCCGCAGATACCCCTGTGAG
TGGGGGGGTGTGGCAGCTGGCCGGCCCTATGTTGGCGGGCTGGAGGAGT
TTGGGCAGTTGGTTCTGCAGGATGTATGGAATATGATCCAGAAGCTCTA
CCTGCAGCCTGGGGCCCTGCTGGAGCAGCCAGTGTCCATCCCAGACGAT
GACTTGGTCCAGGCCACCTTCCAGCAGCTGCAGAAGCCACCGAGTCCTG
CCCGGCCACGCCTTCTTCAGGACACAGTGCAACAGCTGATGCTGCCCCA
CGGAAGGCTGAGCCTGGTGACGGGGCAGTCAGGACAGGGCAAGACAGCC
TTCCTGGCATCTCTTGTGTCAGCCCTGCAGGCTCCTGATGGGGCCAAGG
TGGCACCATTAGTCTTCTTCCACTTTTCTGGGGCTCGTCCTGACCAGGG
TCTTGCCCTCACTCTGCTCAGACGCCTCTGTACCTATCTGCGTGGCCAA
CTAAAAGAGCCAGGTGCCCTCCCCAGCACCTACCGAAGCCTGGTGTGGG

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FIG. 1E

AGCTGCAGCAGAGGCTGCTGCCCAAGTCTGCTGAGTCCCTGCATCCTGG
CCAGACCCAGGTCCTGATCATCGATGGGGCTGATAGGTTAGTGGACCAG
AATGGGCAGCTGATTTTCAGACTGGATCCCAAAGAAGCTTCCCCGGTGTG
TACACCTGGTGCTGAGTGTGTCTAGTGATGCAGGCCTAGGGGAGACCCT
TGAGCAGAGCCAGGGTGCCACGTGCTGGCCTTGGGGCCTCTGGAGGCC
TCTGCTCGGGCCCGGCTGGTGAGAGAGGAGCTGGCCCTGTACGGGAAGC
GGCTGGAGGAGTCACCATTTAACAACCAGATGCGACTGCTGCTGGTGAA
GCGGGAATCAGGCCGGCCGCTCTACCTGCGCTTGGTCACCGATCACCTG
AGGCTCTTCACGCTGTATGAGCAGGTGTCTGAGAGACTCCGGACCCTGC
CTGCCACTGTCCCCCTGCTGCTGCAGCACATCCTGAGCACACTGGAGAA
GGAGCACGGGCCTGATGTCCTTCCCCAGGCCTTGACTGCCCTAGAAGTC
ACACGGAGTGGTTTGACTGTGGACCAGCTGCACGGAGTGCTGAGTGTGT
GGCGGACACTACCGAAGGGGACTAAGAGCTGGGAAGAAGCAGTGGCTGC
TGGTAACAGTGGAGACCCCTACCCCATGGGCCCCGTTTGCCTGCCTCGTC
CAGAGTCTGCGCAGTTTGCTAGGGGAGGGCCCTCTGGAGCGCCCTGGTG
CCCGGCTGTGCCTCCCTGATGGGCCCCCTGAGAACAGCAGCTAAACGTTG
CTATGGGAAGAGGCCAGGGCTAGAGGACACGGCACACATCCTCATTGCA
GCTCAGCTCTGGAAGACATGTGACGCTGATGCCTCAGGCACCTTCCGAA
GTTGCCCTCCTGAGGCTCTGGGAGACCTGCCTTACCACCTGCTCCAGAG

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FIG. 1F

CGGGAACCGTGGACTTCTTTTCGAAGTTCCTTACCAACCTCCATGTGGTG
GCTGCACACTTGGAATTGGGTCTGGTCTCTCGGCTCTTGAGGCCCATG
CCCTCTATGCTTCTTCAGTCCCCAAAGAGGAACAAAAGCTCCCCGAGGC
TGACGTTGCAGTGTTTCGCACCTTCCTGAGGCAGCAGGCTTCAATCCTC
AGCCAGTACCCCCGGCTCCTGCCCCAGCAGGCAGCCAACCAGCCCCTGG
ACTCACCTCTTTGCCACCAAGCCTCGCTGCTCTCCCGGAGATGGCACCT
CCAACACACACTACGATGGCTTAATAAACCCCGGACCATGAAAAATCAG
CAAAGCTCCAGCCTGTCTCTGGCAGTTTCCTCATCCCCTACTGCTGTGG
CCTTCTCCACCAATGGGCAAAGAGCAGCTGTGGGCACTGCCAATGGGAC
AGTTTACCTGTTGGACCTGAGAACTTGGCAGGAGGAGAAGTCTGTGGTG
AGTGGCTGTGATGGAATCTCTGCTTGTTTGTTTCCTCTCCGATGATACAC
TCTTTCTTACTGCCTTCGACGGGCTCCTGGAGCTCTGGGACCTGCAGCA
TGGTTGTCGGGTGCTGCAGACTAAGGCTCACCAGTACCAAATCACTGGC
TGCTGCCTGAGCCCAGACTGCCGGCTGCTAGCCACCGTGTGCTTGGGAG
GATGCCTAAAGCTGTGGGACACAGTCCGTGGGCAGCTGGCCTTCCAGCA
CACCTACCCCAAGTCCCTGAACTGTGTTGCCTTCCACCCAGAGGGGCAG
GTAATAGCCACAGGCAGCTGGGCTGGCAGCATCAGCTTCTTCCAGGTGG
ATGGGCTCAAAGTCACCAAGGACCTGGGGGCACCCGGAGCCTCTATCCG
TACCTTGGCCTTCAATGTGCCTGGGGGGGTGTGGCTGTGGGCCGGCTG

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FIG.1G

GACAGTATGGTGGAGCTGTGGGCCTGGCGAGAAGGGGCACGGCTGGCTG
CCTTCCCTGCCCCACCATGGCTTTGTTGCTGCTGCGCTTTTCCTGCATGC
GGGTTGCCAGTTACTGACGGCTGGAGAGGATGGCAAGGTTTCAGGTGTGG
TCAGGGTCTCTGGGTCGGCCCCGTGGGCACCTGGGTTCCCTTTCTCTCT
CTCCTGCCCTCTCTGTGGCACTCAGCCCAGATGGTGATCGGGTGGCTGT
TGGATATCGAGCGGATGGCATTAGGATCTACAAAATCTCTTCAGGTTCC
CAGGGGGCTCAGGGTCAGGCACTGGATGTGGCAGTGTCCGCCCTGGCCT
GGCTAAGCCCCAAGGTATTGGTGAGTGGTGCAGAAGATGGGTCCTTGCA
GGGCTGGGCACTCAAGGAATGCTCCCTTCAGTCCCTCTGGCTCCTGTCC
AGATTCCAGAAGCCTGTGCTAGGACTGGCCACTTCCCAGGAGCTCTTGG
CTTCTGCCTCAGAGGATTTACAGTGCAGCTGTGGCCAAGGCAGCTGCT
GACGCGGCCACACAAGGCAGAAGACTTTCCCTGTGGCACTGAGCTGCGG
GGACATGAGGGCCCTGTGAGCTGCTGTAGTTTCAGCACTGATGGAGGCA
GCCTGGCCACCGGGGGCCGGGATCGGAGTCTCCTCTGCTGGGACGTGAG
GACACCCAAAACCCCTGTTTTGATCCACTCCTTCCCTGCCTGTCACCGT
GACTGGGTCACTGGCTGTGCCTGGACCAAAGATAACCTACTGATATCCT
GCTCCAGTGATGGCTCTGTGGGGCTCTGGGACCCAGAGTCAGGACAGCG
GCTTGGTCAGTTCCTGGGTCATCAGAGTGCTGTGAGCGCTGTGGCAGCT
GTGGAGGAGCACGTGGTGTCTGTGAGCCGGGATGGGACCTTGAAAGTGT

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FIG. 1H

GGGACCATCAAGGCGTGGAGCTGACCAGCATCCCTGCTCACTCAGGACC
CATTAGCCACTGTGCAGCTGCCATGGAGCCCCGTGCAGCTGGACAGCCT
GGGTCAGAGCTTCTGGTGGTAACCGTCGGGCTAGATGGGGCCACACGGT
TATGGCATCCACTCTTGGTGTGCCAAACCCACACCCTCCTGGGACACAG
CGGCCCAGTCCGTGCTGCTGCTGTTTCAGAAACCTCAGGCCTCATGCTG
ACCGCCTCTGAGGATGGTTCTGTACGGCTCTGGCAGGTTCTTAAGGAAG
CAGATGACACATGTATACCAAGGAGTTCTGCAGCCGTCACTGCTGTGGC
TTGGGCACCAGATGGTTCCATGGCAGTATCTGGAAATCAAGCTGGGGAA
CTAATCTTGTGGCAGGAAGCTAAGGCTGTGGCCACAGCACAGGCTCCAG
GCCACATTGGTGCTCTGATCTGGTCCTCGGCACACACCTTTTTTGTCTCT
CAGTGCTGATGAGAAAATCAGCGAGTGGCAAGTGAAACTGCGGAAGGGT
TCGGCACCCGGAAATTTGAGTCTTCACCTGAACCGAATTCTACAGGAGG
ACTTAGGGGTGCTGACAAGTCTGGATTGGGCTCCTGATGGTCACTTTCT
CATCTTGGCCAAAGCAGATTTGAAGTTACTTTGCATGAAGCCAGGGGAT
GCTCCATCTGAAATCTGGAGCAGCTATACAGAAAATCCTATGATATTGT
CCACCCACAAGGAGTATGGCATATTTGTCTCTGCAGCCCAAGGATCCTGG
AGTTCTTTCTTTCTTGAGGCAAAGGAATCAGGAGAGTTTGAAGAGAGG
CTGAACTTTGATATAAACTTAGAGAATCCTAGTAGGACCCTAATATCGA
TAACTCAAGCCAAACCTGAATCTGAGTCCTCATTTTTTGTGTGCCAGCTC

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FIG. 11

TGATGGGATCCTATGGAACCTGGCCAAATGCAGCCCAGAAGGAGAATGG
ACCACAGGTAACATGTGGCAGAAAAAAGCAAACACTCCAGAAACCCAAA
CTCCAGGGACAGACCCATCTACCTGCAGGGAATCTGATGCCAGCATGGA
TAGTGATGCCAGCATGGATAGTGAGCCAACACCACATCTAAAGACACGG
CAGCGTAGAAAGATTCACTCGGGCTCTGTACAGCCCTCCATGTGCTAC
CTGAGTTGCTGGTGACAGCTTCGAAGGACAGAGATGTTAAGCTATGGGA
GAGACCCAGTATGCAGCTGCTGGGCCTGTTCCGATGCGAAGGGTCAGTG
AGCTGCCTGGAACCTTGGCTGGGCGCTAACTCCACCCTGCAGCTTGCCG
TGGGAGACGTGCAGGGCAATGTGTACTTTCTGAATTGGGAA

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FIG.2A

ATGGAGAAGCTCTGTGGGCATGTGCCTGGCCATTGAGACATCCTCTCCT
TGAAGAACCGGTGCCTGACCATGCTCCCTGACCTCCAGCCCCTGGAGAA
AATACATGGACATAGATCTGTCCACTCAGACATCCTTTTCCTTGGAGAAC
CAGTGTCTGACCATGCTCTCTGACCTCCAGCCCACGGAGAGAATAGATG
GGCATATATCTGTCCACCCAGACATCCTCTCCTTGGAGAATCGGTGCCT
GACCATGCTCCCTGACCTCCAGCCTCTGGAGAAGCTATGTGGACATATG
TCTAGTCATCCAGACGTCCTTTCTTTGGAAAACCAATGTCTAGCTACTC
TCCCCACTGTAAAGAGCACTGCATTGACCAGCCCCTTGCTCCAGGGTCT
TCACATATCTCATAACGGCACAAGCTGATCTGCATAGCCTGAAAACCTAGC
AACTGCCTGCTCCCTGAGCTTCCTACCAAGAAGACTCCATGTTTCTCTG
AGGAACTAGACCTTCCACCTGGACCCAGGGCCCTGAAATCCATGTCTGC
TACAGCTCAAGTCCAGGAAGTAGCCTTGGGTCAATGGTGTGTCTCCAAA
GAAAAGGAATTTCAAGAAGAAGAAAGCACAGAAGTCCCRATGCCTTTGT
ACAGTCTAAGCTTGGAAGAAGAAGAAGTGGAGGCACCGGTCTTAAACT
CACATCTGGAGACTCTGGCTTTCATCCTGAAACCACTGACCAGGTCCTT
CAGGAGAAGAAGATGGCTCTCTTGACCTTACTCTGCTCTGCTCTGGCCT
CAAATGTGAATGTGAAAGATGCATCTGACCTTACCCGGGCATCCATCCT
TGAAGTCTGTAGTGCCCTGGCCTCCTTGGAACCGGAGTTCATCCTTAAG
GCATCTTTGTATGCTCGGCAGCAACTTAACCTCCGGGACATCGCCAATA

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FIG.2B

CAGTTCTGGCTGTGGCTGCCCTCTTGCCAGCCTGCCGCCCCCATGTACG
ACGGTATTACTCCGCCATTGTTACCTGCCTTCAGACTGGATCCAGGTA
GCCGAGTTCTACCAGAGCCTGGCAGAAGGGGATGAGAAGAAGTTGGTGT
CCCTGCCTGCCTGTCTCCGAGCTGCCATGACCGACAAATTTGCCGAGTT
TGATGAGTACCAGCTAGCTAAGTACAACCCACGGAAACATCGGTCCAAG
AGGCGGTCCCGCCAGCCACCCCGCCCTCAAAGACAGAACGTCCATTTT
CAGAGAGAGGGAAATGTTTTCCAAAGAGCCTTTGGCCCCCTAAAAATGA
ACAGATTACGTTTGAAGCAGCTTATAATGCAATGCCAGAGAAAAACAGG
CTACCACGGTTCACTCTGAAGAAGTTGGTAGAGTATCTACATATCCACA
AGCCTGCTCAGCACGTCCAGGCCCTGCTGGGCTACAGGTACCCAGCCAC
CCTAGAGCTCTTTTCTCGGAGTCACCTCCCTGGGCCGTGGGAGTCTAGC
AGAGCTGGTCAGCGGATGAAGCTCCGAAGGCCAGAGACCTGGGAGCGGG
AGCTGAGTTTACGGGGAAACAAAGCTTCTGTGTGGGAGGAGCTCATAGA
CAATGGGAAACTGCCCTTCATGGCCATGCTCCGGAACCTGTGTAACCTG
CTGCGGACTGGGATCAGTGCCCGCCACCATGAACTCGTTCTCCAGAGAC
TCCAGCATGAGAAATCTGTGGTTCACAGTCGGCAGTTTCCATTTCAGATT
CCTTAATGCTCATGACTCTATCGATAAACTTGAGGCTCAGCTCAGAAGC
AAAGCATCACCCCTTCCCTTCCAATACAACATTGATGAAACGGATAATGA
TTAGAAACTCAAAAAAAAAATAGGAGGCCTGCCAGTCGGAAGCACCTGTG

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FIG.2C

CACCCTGACGCGCCGGCAGCTTCGGGCAGCAATGACTATACCTGTGATG
TATGAGCAGCTCAAGCGGGAGAACTGAGGCTGCACAAGGCCAGACAAT
GGAActGTGATGTTGAGTTGCTGGAGCGCTATCGCCAGGCCCTGGAAAC
AGCTGTGAACCTCTCAGTAAAGCACAACTATCCCCGATGCCTGGCCGA
ACCCTCTTGGTCTATCTCACAGATGCAAATGCCGACAGGCTCTGTCCCA
AGAGTCACTCACAAGGGCCTCCCCTGAACTATGTGCTGCTGCTGATCGG
AATGATGGTGGCTCGAGCCGAGCAAGTGAAGTGTGCTTGTGTGGGGGA
GGATTTGTGAAGACACCGGTACTTACAGCCGATGAAGGCATCCTGAAGA
CTGCCATCAAAC⁵TCAGGCTCAAGTCCAGGAGTTAGAAGGCAATGATGA
GTGGCCCCCTGGACACTTTTGGGAAGTATCTGCTGTCTCTGGCTGTCCAA
AGGACCCCCCATTGACAGGGTCATCCTGTTTGGTCAAAGGATGGATACCG
AGCTCCTGAAAGTAGCCAAACAGATTATCTGGCAGCATGTGAATTCCAA
GTGCCTCTTTGTTGGTGTCTCCTACAGAAAACACAGTACATATCACCA
AATTTGAATCCCAACGATGTGACGCTCTCAGGCTGCACTGACGGGATCC
TGAAATTCATTGCCGAACATGGAGCCTCTCGTCTCCTGGAACATGTGGG
ACAACTAGATAAACTATTCAAGATCCCCCACC⁵CCAGGAAAGACACAG
GCACCGTCTCTCCGGCCGCTGGAGGAGAACATCCCTGGTCCCTTGGGTC
CTATTTCCCAGCATGGATGGCGCAATATCCGGCTTTTCATTTTCATCCAC
TTTCCGTGACATGCATGGGGAGCGAGATTTGCTGATGAGATCTGTTCTG

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FIG.2D

CCCGCACTGCAGGCCAGAGTGTTCCCCCACCGCATCAGTCTTCACGCCA
TTGACCTGCGCTGGGGTATCACAGAGGAAGAGACCCGCAGGAACAGACA
ACTGGAAGTGTGCCTTGGGGAGGTGGAGAACTCACAGCTGTTTCGTGGGG
ATTCTGGGCTCCCGCTATGGCTACATTCCCCCAGCTATGATCTTCCTG
ATCATCCCCACTTTCAGTGGACCCATGAGTACCCTTCAGGGCGATCCGT
GACAGAGATGGAGGTGATGCAATTCCCTGAACCGTGGCCAACGCTCGCAG
CCTTCGGCCCAAGCTCTCATCTACTTCCGAGATCCTGATTTTCCTTAGCT
CTGTGCCAGATGCCTGGAAACCTGACTTTATATCTGAGTCAGAAGAAGC
TGCACATCGGGTCTCAGAGCTGAAGAGATATCTACACGAACAGAAAGAG
GTTACCTGTTCGAGCTACTCCTGTGAATGGGGAGGTGTAGCGGCTGGCC
GGCCCTATACTGGGGGCCTGGAGGAGTTTGGACAGTTGGTTCTCCAGGA
TGTGTGGAGCATGATCCAGAAGCAGCACCTGCAGCCTGGGGCCCAGTTG
GAGCAGCCAACATCCATCTCAGAAGACGATTTGATCCAGACCAGCTTTC
AGCAGCTGAAGACCCCAACGAGTCCGGCACGGCCACGCCTTCTTCAGGA
TACAGTGCAGCAGCTGTTGCTGCCCCATGGGAGGCTGAGCCTAGTGACT
GGGCAGGCAGGACAGGGAAAGACTGCCTTTCTGGCATCCCTTGTGTCTG
CCCTGAAGGTCCCTGACCAGCCCAATGAGCCCCCGTTTCGTTTTCTTCCA
CTTTGCAGCAGCCCGCCCTGACCAGTGTCTTGCTCTCAACCTCCTCAGA
CGCCTCTGTACCCATCTGCGTCAAAAAGTGGGAGAGCTGAGTGCCCTCC

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FIG.2E

CCAGCACTTACAGAGGCCTGGTGTGGGAACTGCAGCAGAAGTTGCTCCT
CAAATTCGCTCAGTCGCTGCAGCCTGCTCAGACTTTGGTCCTTATCATC
GATGGGGCAGATAAGTTGGTGGATCGTAATGGGCAGCTGATTTTCAGACT
GGATCCCCAAGTCTCTTCCGCGGCGAGTACACCTGGTGCTGAGTGTGTC
CAGTGA CT CAGGCCTGGGTGAGACCCCTTCAGCAAAGTCAGGGTGCTTAT
GTGGTGGCCTTGGGCTCTTTGGTCCCATCTTCAAGGGCTCAGCTTGTGA
GAGAAGAGCTAGCACTGTATGGGAAACGACTGGAGGAGTCACCTTTTAA
CAACCAGATGCGGCTGCTGCTGGCAAAGCAGGGTTCAAGCCTGCCATTG
TACCTGCACCTTGTC ACT GACTACCTGAGGCTCTTCACACTGTATGAAC
AGGTGTCTGAGAGACTTCGAACCCTGCCCCGCACTCTCCCACTGCTCTT
GCAGCACATCCTGAGCACCTTGAGCAAGAACATGGCCATGATGTCCTT
CCTCAGGCTTTGACTGCCCTTGAGGTCACACGAAGTGGTCTGACTGTGG
ACCAGCTACATGCAATCCTGAGCACATGGCTGATCTTGCCCAAGGAGAC
TAAGAGCTGGGAAGAAGTGCTGGCTGCCAGTCACAGTGGA AACCTTTC
CCCTTGTGTCCATTTGCCTACCTTGTCCAGAGTCTACGCAGTTTACTAG
GGGAGGGCCCAGTGGAGCGCCCTGGTGCCCGTCTCTGCCTCTCTGATGG
GCCCCTGAGGACAACAATTAAACGTCGCTATGGGAAAAGGCTGGGGCTA
GAGAAGACTGCGCATGTCCTCATTGCAGCTCACCTCTGGAAGACGTGTG
ATCCTGATGCCTCGGGCACCTTCCGAAGTTGCCCTCCTGAGGCTCTGAA

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FIG.2F

AGATTTACCTTACCACCTGCTCCAGAGCGGGAACCATGGTCTCCTTGCC
GAGTTTCTTACCAATCTCCATGTGGTTGCTGCATATCTGGAAGTGGGTC
TAGTCCCCGACCTCTTGGAGGCTCATGTGCTCTATGCTTCTTCAAAGCC
TGAAGCCAACCAGAAGCTCCCAGCGGCAGATGTTGCTGTTTTCCATACC
TTCCTGAGACAACAGGCTTCACTCCTTACCCAGTATCCTTTGCTCCTGC
TCCAGCAGGCAGCTAGCCAGCCTGAAGAGTCACCTGTTTGCTGCCAGGC
CCCCCTGCTCACCCAGCGATGGCACGACCAGTTCACACTGAAATGGATT
AATAAACCCCAGACCCTGAAGGGTCAGCAAAGCTTGCTCTCTGACAATGT
CCTCATCCCCAAGTGTGTGGCCTTCTCCCCGAATGGGCAAAGAGCAGC
TGTGGGGACCGCCAGTGGGACAATTTACCTGTTGAACTTGAAAACCTGG
CAGGAGGAGAAGGCTGTGGTGAGTGGCTGTGACGGGATTTCTCTTTTG
CATTCCTTTTCGGACACTGCCCTTTTCCTTACTACCTTCGACGGGCACCT
AGAGCTTTGGGACCTGCAACATGGTTGTTGGGTGTTTCAGACCAAGGCC
CACCAGTACCAAATCACTGGCTGCTGCCTGAGCCCAGACCGCCGCCTGC
TGGCCACTGTGTGTTTGGGAGGATACCTAAAGCTGTGGGACACAGTCCG
AGGACAGCTGGCTTTTTCAGTACACCCATCCAAAGTCTCTCAACTGCGTT
GCCTTCCACCCAGAGGGGCAGGTGGTAGCCACAGGCAGCTGGGCTGGCA
GCATTACCTTCTTCCAGGCAGATGGACTCAAAGTCACCAAGGAACTAGG
GGCCCCCGGACCCTCTGTCTGTAGTTTGGCATTCACAAACCTGGGAAG

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FIG.2G

ATTGTGGCTGTGGGCCGGATAGATGGGACAGTGGAGCTGTGGGCCTGGC
AAGAGGGTGCCCGGCTGGCGGCCTTCCCTGCACAGTGTGGCTGTGTCTC
TGCTGTTCTTTTCTTGCACTGCTGGAGACCGGTTCTGACTGCTGGAGAA
GATGGCAAGGCTCAGTTATGGTCAGGATTTCTTGGCCGGCCCAGGGGTT
GCCTGGGCTCTCTTCCCTCTTTCTCCTGCACTCTCGGTGGCTCTCAACCC
AGACGGTGACCAGGTGGCTGTTGGGTACCGAGAAGATGGCATTAAACATC
TACAAGATTTCTTCAGGTTCCCAGGGGCCTCAGCATCAAGAGCTAAATG
TGGCGGTGTCTGCACTGGTGTGGCTGAGCCCTAGTGTTTTGGTGAGTGG
TGCAGAAGATGGATCCCTGCATGGTTGGATGTTCAAGGGAGACTCCCTT
CATTCCTGTGGCTGTTGTGCGAGATAACCAGAAGCCTGTGCTGGGACTGG
CTGCCTCCCGGGAACATCATGGCTGCTGCCTCAGAGGACTTCACTGTGAG
ACTGTGGCCCAGACAGCTGCTGACACAGCCACATGTGCATGCGGTAGAG
TTGCCCTGTTGTGCTGAACTCCGGGGACACGAGGGGCCAGTGTGCTGCT
GTAGCTTCAGCCCTGATGGAGGCATCTTGGCCACAGCTGGCAGGGATCG
GAATCTCCTTTGCTGGGACATGAAGATAGCCCAAGCCCCTCTCCTGATT
CACACTTTCTCGTCCTGTCATCGTGACTGGATCACTGGCTGTGCGTGGA
CCAAAGACAACATCCTGGTCTCCTGCTCGAGTGATGGCTCTGTGGGACT
CTGGAACCCAGAGGCAGGGCAGCAACTTGGCCAGTTCTCAGGCCACCAG
AGTGCCGTGAGCGCCGTGGTTGCTGTGGAGGAACACATTGTATCTGTGA

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FIG.2H

GCCGAGATGGGACCTTGAAAGTGTGGGACCATCAGGGTGTGGAGCTGAC
CAGCATCCCTGCCCATTCCGGACCCATCAGCCAGTGTGCAGCTGCTCTG
GAGCCCCGCCCAGGGGGACAGCCTGGATCAGAGCTTCTGGTGGTGACTG
TTGGACTAGATGGGGCCACAAAGTTGTGGCATCCCCTGTTGGTGTGCCA
AATACGTACTCTCCAGGGACACAGTGGCCCAGTCACAGCAGCTGCTGCT
TCAGAGGCCTCAGGCCTCCTGCTGACCTCAGATGATAGCTCTGTACAGC
TCTGGCAGATACCAAAGGAAGCAGATGATTCATACAAACCTAGGAGTTC
TGTGGCCATCACTGCTGTGGCATGGGCACCGGATGGTTCTATGGTGGTG
TCCGGAAATGAAGCCGGGGAAGTGAACACTGTGGCAGCAAGCCAAGGCTG
TGGCTACCGCACAGGCTCCAGGCCGCGTCAGTCACCTGATCTGGTACTC
GGCAAATTCATTCTTCGTTCTCAGTGCTAATGAAAACGTCAGCGAGTGG
CAAGTGGGACTGAGGAAAGGTTCAACGTCCACCAGTTCCAGTCTTCATC
TGAAGAGAGTTCTGCAGGAGGACTGGGGAGTCTTGACAGGTCTGGGTCT
GGCCCCTGATGGCCAGTCTCTCATCTTGATGAAAGAGGATGTGGAATTA
CTAGAGATGAAGCCTGGGTCTATTCCATCTTCTATCTGCAGGAGGTATG
GAGTACATTCTTCAATACTGTGCACCAGCAAGGAGTACGGCTTGTTCTA
CCTGCAGCAGGGGGACTCCGGATTACTTTCTATATTGGAGCAAAGGAG
TCAGGGGAGTTTGAAGAGATCCTGGACTTCAATCTGAACTTAAATAATC
CTAATGGGTCCCCAGTATCAATCACTCAGGCCAAACCTGAGTCTGAATC

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FIG. 21

ATCCCTTTTGTGCGCCACCTCTGATGGGATGCTGTGGAACCTTATCTGAA
TGTACCTCAGAGGGAGAATGGATCGTAGATAACATTTGGCAGAAAAAAG
CAAAAAACCTAAAACTCAGACTCTGGAGACAGAGTTGTCCCCGCACTC
AGAGTTGGATTTTTCCATTGATTGCTGGATTGATCCCACAAATTTAAAG
GCACAGCAGTGTA AAAAGATCCACTTGGGCTCTGTACAGCCCTCCATG
TGCTTCCGGGATTGCTGGTGACAGCTTCGAAGGACAGAGATGTTAAGCT
GTGGGAGAGACCCAGTATGCAGCTGCTGGGCTTGTTCCGATGTGAAGGG
CCAGTGAGCTGTCTGGAACCTTGATGGAGCCCAGCTCTCCCCTGCAGC
TTGCTGTGGGAGACACACAAGGAAACTTGTATTTTCTATCTTGGGAA

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FIG.3A

MEKLHGHVSAHPDILSLENRCLAMLPDLQPLEKLHQHVSTHSDILSLKN
QCLATLPDLKTMEKPHGYVSAHPDILSLENQCLATLSDLKTMEKPHGHV
SAHPDILSLENRCLATLPSTKSTVSASPLFQSLQISHMTQADLYRVNNS
NCLLSEPPSWRAQHFSKGLDLSTCPIALKSISATETAQEATLGRWFDSE
EKKGAEQTOMPSYSLSLGEEEEVEDLAVKLTSGDSESHPEPTDHVLQEEK
MALLSLLCSTLVSEVNMNNTSDPTLAAIFEICRELALLEPEFILKASLY
ARQQLNVRNVANNILAIAAFLPACRPHLRRYFCAIVQLPSDWIQVAELY
QSLAEGDKNKLVPLPACLRRTAMTDKFAQFDEYQLAKYNPRKHKRAKRHPR
RPPRSPGMEPPFSSHRCFPRYIGFLREEQRKFEEKAGDTVSEKKNPPRFTL
KKLVQRLHIHKPAQHVQALLGYRYPNQLFSSRLPGPWDSSRAGKRM
KLSRPETWERELSLRGNKASVWEELIENGKLPFMAMLRNLCNLLRVGIS
SRHHELILQRLQHGKSVIHSRQFPFRFLNAHDAIDALEAQLRNQALPFP
SNITLMRRILTRNEKNRPRRRFLCHLSRQQLRMAMRIPVLYEQLKREKL
RVHKARQWKYDGEMLNRYRQALETAVNLSVKHSLPLLPGRTVLVYLTDA
NADRLCPKSNPQGPPPLNYALLLIGMMITRAEQVDVVLGGDTLKTAVLK
AEEGILKTAIKLQAQVQEFDENDGWSLNTFGKYLLSLAGQRPVDRVIL
LGQSMDDGMINVAKQLYWQRVNSKCLFVGILLRRVQYLSTDLPNDVTL
SGCTDAILKFIAEHGASHLLEHVGQMDKIFKIPPPGKTGVQSLRPLEE
DTPSPLAPVSQQGWRISIRLFISSTFRDMHGERDLLRSVLPALQARAAP

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FIG.3B

HRISLHGIDLRWGVTEETRRNRQLEVCLGEVENAQLFVGILGSRYGYI
PPSYNLPDHPHFHWAQQYPSGRSVTEMEVMQFLNRNQRLQPSAQUALIYF
RDSSFLSSVPDAWKSDVFVSESEEAAXRISELKSYLSRQKGITCRRYPCE
WGGVAAGRPYVGGLEEFQQLVLQDVWNMIQKLYLQPGALLEQPVSIIPDD
DLVQATFQQLQKPPSPARPRLLQDTVQXLMLPHGRSLSVTGQSGQGKTA
FLASLVSAHQAPDGAKVAXLVFFHFSGARPDQGLALTLLRRLCTYLRGQ
LKEPGALPSTYRSLVWELQQRLLPKSAESLHPGQTQVLIIDGADRLVDQ
NGQLISDWIPKKLPRCVHLVLSVSSDAGLGETLEQSQGAHVLAALGPlea
SARARLVREELALYGKRLEESPFNNQMRLLLVKRESGRPLYLRLVTDHL
RLFTLYEQVSERLRTLTPATVPLLLQHILSTLEKEHGPDLVPQALTALEV
TRSGLTVDQLHGVLSVWRTLPGKTKSWEEAVAAGNSGDPYPMGPFACLV
QSLRSLLGEGPLERPGARLCLPDGPLRTAAKRCYGKRPGLEDTAHILIA
AQLWKTCADADASGTFRSCPPEALGDLPHYLLQSGNRGLLSKFLTNLHVV
AAHLELGLVSRLLLEAHALYASSVPKEEQKLPEADVAVFRTFLRQQASIL
SQYPRLLPQQAANQPLDSPLCHQASLLSRRWHLQHTLRWLNKPRTMKNQ
QSSSLSLAVSSSPTAVAFSTNGQRAAVGTANGTVYLLDLRTWQEEKSVV
SGCDGISACLFLSDDTLFLTAFDGLLELWDLQHGCRLVQTKAHQYQITG
CCLSPDCRLLATVCLGGCLKLWDTVRGQLAFQHTYPKSLNCVAFHPEGQ
VIATGSWAGSISFFQVDGLKVTKDLGAPGASIRTLAFNVPGGVAVGRL

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FIG.3C

DSMVELWAWREGARLAAFPAPHHGFVAAALFLHAGCQLLTAGEDGKVQVW
SGSLGRPRGHLGSLSLSPALSVALSPDGDRVAVGYRADGIRIYKISSGS
QGAQGOALDVAVSALAWLSPKVLVSGAEDGSLQGWLKECSLQSLWLLS
RFQKPVLGLATSQELLASASEDFTVQLWPRQLLTRPHKAEDFPCGTELR
GHEGPVSCCSFSTDGGSLATGGRDRSLLCWDVVRTPKTPVLIHSFPACHR
DWVTGCAWTKDNLLISCSSDGSVGLWDPESGQRLGQFLGHQSAVSAVAA
VEEHVSVSRDGTCLKVWDHQGVELTSIPAHSGPISHCAAAMEPRAAGQP
GSELLVVTVGLDGATRLWHPLLVQCQHTLLGHSGPVRAAAVSETSGMLL
TASEDGSVRLWQVPKEADDTICIPRSSAAVTAVAWAPDGSMASVSGNQAGE
LILWQEAKAVATAQAPGHIGALIWSSAHTFFVLSADEKISEWQVKLRKG
SAPGNLSLHLNRILQEDLGVLTSLDWAPDGHFLILAKADLKLKCMKPGD
APSEIWSSYTENPMILSTHKEYGIFVLQPKDPGVLSFLRQKESGEFEER
LNF DINLENPSRTLISITQAKPESESSFLCASSDGILWNLAKCSPEGEW
TTGNMWQKKANTPETQTPGTDPSTCRESDASMDSDASMDSEPTPHLKTR
QRRKIHSGSVTALHVLPELLVTASKDRDVKLWERPSMQLLGLFRCEGSV
SCLEPWLGANSTLQLAVGDVQGNVYFLNWE

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FIG.4A

MEKLCGHVPGHSDILSLKNRCLTMLPDLQPLEKIHGHRSVHSDILSLEN
QCLTMLSDLQPTERIDGHISVHPDILSLENRCLTMLPDLQPLEKLCGHM
SSHDPVLSLENQCLATLPTVKSTALTSPLLQGLHISHTAQADLHSLKTS
NCLLPELPTKKTPCFSEELDLP GPRAK SMSATAQVQEVALGQWCVSK
EKEFQEEESTEVPMPLYSLSEEEEEVEAPVLKLTSGDSGFHPETTDQVL
QEKKMALLTLLCSALASNVNVKDASDLTRASILEVCSALASLEPEFILK
ASLYARQQNLNRDIANTVLAVAALLPACRPHVRRYYS AIVHLPSDWIQV
AEFYQSLAEGDEKKLVSLPACLRAAMTDKFAEFDEYQLAKYNPRKHSK
RRSRQPPRPQKTERPF SERGKCFPKSLWPLKNEQITFEAAYNAMPEKNR
LPRFTLKKLVEYLHIHKPAQHVQALLGYRYPATLELFSRSHLPGPWESS
RAGQRMKLRRPETWERELSLRGNKASVWEELIDNGKLPFMAMLRNLCNL
LRTGISARHHELVLQRLQHEKSVVHSRQFPFRFLNAHDSIDKLEAQLRS
KASPFPSNTTLMKRIMIRNSKKNRRPASRKHLCTLTRRQLRAAMTIPVM
YEQLKREKLRLHKARQWNC DVELLERYRQALETAVNLSVKHNLS PMPGR
TLLVYLTDANADRLCPKSHSQGPPLNYVLLLLIGMMVARAEQVTVCLCGG
GFVKTPVLTADEGILKTAIKLQAQVQEELEGNDEWPLDFTGKYLLSLAVQ
RTPIDRVILFGQRMDELLKVAQIIWQHVN SKCLFVGVLLOKTQYISP
NLNPNDVTL SGCTDGILKFIAEHGASRLLEHVGQLDKLFKIPPPGKTQ
APSLRPLEENIPGPLGPISQHGWRNIRLFISSTFRDMHGERDLLMRSVL

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FIG.4B

PALQARVFPHRISLHAIDLRWGITEEETRRNRQLEVCLGEVENSQLFVG
ILGSRYGYIPPSYDLDPDHPHFHWTHEYPSGRSVTEMEVMQFLNRGQRSQ
PSAQALIYFRDPDFLSSVPDAWKPDFISESEEAHRVSELKRYLHEQKE
VTCRSYSCEWGGVAAGRPYTGGLLEFGQLVLQDVWSMIQKQHLQPGAQL
EQPTSISEDCLIQTSFQQLKTPTSPARPRLLQDTVQQLLLPHGRLSLVT
GQAGQGKTAFLASLVSALKVPDQPNPPFVFFHFAAARPDQCLALNLLR
RLCTHLRQKLGELSALPSTYRGLVWELQQKLLLKFAQSLQPAQTLVLI
DGADKLVDNRNGQLISDWIPKSLPRRVHLVLSVSSDSGLGETLQQSQGAY
VVALGSLVPSSRAQLVREELALYGKRLEESPFNNQMRLLAKQGSSPL
YLHLVTDYLRFLTLYEQVSERLRTLPLTLPLLLQHILSTLEQEHGHDVL
PQALTALEVTRSGLTVDQLHAILSTWLILPKETKSWEVLAASHSGNPF
PLCPFAYLVQSLRSLLGEGPVERPGARLCLSDGPLRTTIKRRYGKRLGL
EKTAHVLIAAHLWKTCDPDASGTFRSCPPEALKDLPYHLLQSGNHGLLA
EFLTNLHVVAAYLEVGLVPDLLEAHVLYASSKPEANQKLPAADVAVFHT
FLRQQASLLTQYPLLLLQQAASQPEESPVCCQAPLLTQRWHDQFTLKWI
NKPQTLKGQQSLSLTMSSSPTAVAFSPNGQRAAVGTASGTIYLLNLKWT
QEEKAVVSGCDGISSFAFLSDTALFLTTFDGHLELWDLQHGCWVFQTKA
HQYQITGCCLSPDRLLATVCLGGYLKLWDTVRGQLAFQYTHPKSLNCV
AFHPEGQVVATGSWAGSITFFQADGLKVTKELGAPGPSVCSLAFNKP GK

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FIG.4C

IVAVGRIDGTVELWAWQEGARLAAPPAQCGCVSAVLFLHAGDRFLTAGE
DGKAQLWSGFLGRPRGCLGSLPLSPALSVALNPDGDQVAVGYREDGINI
YKISSGSQGPQHQLNVAVSALVWLSPSVLVSGAEDGSLHGWFMFKGDSL
HSLWLLSRYQKPVLGLAASRELMAAASEDFTVRLWPRQLLTQPHVHAVE
LPCCAELRGHEGPVCCCSFSPDGGILATAGRDRNLLCWDMKIAQAPLLI
HTFSSCHRDWITGCAWTKDNILVSCSSDGSVGLWNPEAGQQLGQFSGHQ
SAVSAVVAVEEHIVSVSRDGTKVWDHQVELTSIPAHS GPISQCAAAL
EPRPGGQPGSELLVVTVGLDGATKLWHPLLVCQIRTLQGHSGPVTAAAA
SEASGLLLTSDDSSVQLWQIPKEADDSYKPRSSVAITAVAWAPDGSMVV
SGNEAGELTLWQQAKAVATAQAPGRVSHLIWYSANSFFVLSANENVSEW
QVGLRKGSTSTSSSLHLKRVLQEDWGVLTGLGLAPDGQSLILMKEDVEL
LEMKPGSIPSSICRRYGVHSSILCTSKEYGLFYLQQGDSGLLSILEQKE
SGEFEEILDFNLNLNNPNNGSPVSITQAKPESESSLLCATSDGMLWNLSE
CTSEGEWIVDNIWQKKAKKPKTQTLETELSPHSELDFSIDCWIDPTNLK
AQQCKKIHLGSVTALHVLPGLLVTASKDRDVKLWERPSMQLLGLFRCEG
PVSCLEPWMEPSSPLQLAVGDTQGNLYFLSWE

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FIG.5A

CACGCGTCCGGGCAGCGCTGCGTCCTGCTGCGCACGTGGGAAGCCCTGG
CCCCGGCCACCCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCGTGCG
CTCCCTGCTGCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTC
GTGCGGCGCCTGGGGCCCCAGGGCTGGCGGCTGGTGACGCGCGGGGACC
CGGCGGCTTTCCGCGCGCTGGTGGCCCAAGTGCCTGGTGTGCGTGCCCTG
GGACGCACGGCCGCCCCCGCCGCCCCCTCCTTCCGCCAGGTGTCCTGC
CTGAAGGAGCTGGTGGCCCGAGTGCTGCAGAGGCTGTGCGAGCGCGGCG
CGAAGAACGTGCTGGCCTTCGGCTTCGCGCTGCTGGACGGGGCCCCGCGG
GGGCCCCCCCCGAGGCCTTCACCACCAGCGTGCGCAGCTACCTGCCCAAC
ACGGTGACCGACGCACTGCGGGGGAGCGGGGCGTGGGGGCTGCTGCTGC
GCCGCGTGGGCGACGACGTGCTGGTTACCTGCTGGCACGCTGCGCGCT
CTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCCG
CTGTACCAGCTCGGCGCTGCCACTCAGGCCCGGCCCCCGCCACACGCTA
GTGGACCCCGAAGGCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGT
CAGGGAGGCCGGGGTCCCCCTGGGCCTGCCAGCCCCGGGTGCGAGGAGG
CGCGGGGGCAGTGCCAGCCGAAGTCTGCCGTTGCCCAAGAGGCCCAGGC
GTGGCGCTGCCCCCTGAGCCGGAGCGGACGCCCGTTGGGCAGGGGTCCTG
GGCCACCCGGGCAGGACGCGTGACCGAGTGACCGTGGTTTCTGTGTG
GTGTCACCTGCCAGACCCGCCGAAGAAGCCACCTCTTTGGAGGGTGCGC

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FIG.5B

TCTCTGGCACGCGCCACTCCCACCCATCCGTGGGCGCCAGCACCACGC
GGGCCCCCATCCACATCGCGGCCACCACGTCCCTGGGACACGCCTTGT
CCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTCAGGCGACA
AGGAGCAGCTGCGGCCCTCCTTCCTACTCAGCTCTCTGAGGCCCAGCCT
GACTGGCGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCAGGCCC
TGGATGCCAGGGACTCCCCGCAGGTTGCCCCGCCTGCCCCAGCGCTACT
GGCAAATGCGGCCCTGTTTCTGGAGCTGCTTGGAACCACGCGCAGTG
CCCCTACGGGGTGCTCCTCAAGACGCACTGCCCCGCTGCGAGCTGCGGTC
ACCCCAGCAGCCGGTGTCTGTGCCCCGGGAGAAGCCCCAGGGCTCTGTGG
CGGCCCCCGAGGAGGAGGACACAGACCCCCGTCGCCTGGTGCAGCTGCT
CCGCCAGCACAGCAGCCCCTGGCAGGTGTACGGCTTCGTGCGGGCCTGC
CTGCGCCGGCTGGTGCCCCCAGGCCTCTGGGGCTCCAGGCACAACGAAC
GCCGCTTCCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCATGC
CAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCGGGACTGC
GCTTGGCTGCGCAGGAGCCCAGGGGTGGCTGTGTTCCGGCCGCAGAGC
ACCGTCTGCGTGAGGAGATCCTGGCCAAGTTCCTGCACTGGCTGATGAG
TGTGTACGTCGTCGAGCTGCTCAGGTCTTTCTTTTATGTCACGGAGACC
ACGTTTCAAAGAACAGGCTCTTTTCTACCGGAAGAGTGTCTGGAGCA
AGTTGCAAAGCATTGGAATCAGACAGCACTTGAAGAGGGTGACAGCTGCG

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FIG.5C

GGAGCTGTCGGAAGCAGAGGTCAGGCAGCATCGGGAAGCCAGGCCCCGCC
CTGCTGACGTCCAGACTCCGCTTCATCCCCAAGCCTGACGGGCTGCGGC
CGATTGTGAACATGGACTACGTCGTGGGAGCCAGAACGTTCCGCAGAGA
AAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACTGTTACAGCGTG
CTCAACTACGAGCGGGCGCGGCGCCCCGGCCTCCTGGGCGCCTCTGTGC
TGGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGT
GCGGGCCCAGGACCCGCCGCCTGAGCTGTACTTTGTCAAGGTGGATGTG
ACGGGCGCGTACGACACCATCCCCCAGGACAGGCTCACGGAGGTCATCG
CCAGCATCATCAAACCCAGAACACGTA CTGCGTGCGTCCGTATGCCGT
GGTCCAGAAGGCCGCCCATGGGCACGTCCGCAAGGCCTTCAAGAGCCAC
GTCTCTACCTTGACAGACCTCCAGCCGTACATGCGACAGTTCGTGGCTC
ACCTGCAGGAGACCAGCCCGCTGAGGGATGCCGTCGTCATCGAGCAGAG
CTCCTCCCTGAATGAGGCCAGCAGTGGCCTCTTCGACGTCTTCCTACGC
TTCATGTGCCACCACGCCGTGCGCATCAGGGGCAAGTCCTACGTCCAGT
GCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCTGCAGCCT
GTGCTACGGCGACATGGAGAACAAGCTGTTTGCGGGGATTTCGGCGGGAC
GGGCTGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACC
TCACCCACGCGAAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGA
GTATGGCTGCGTGGTGAAC TTGCGGAAGACAGTGGTGAAC TTCCCTGTA

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FIG.5D

GAAGACGAGGCCCTGGGTGGCACGGCTTTTGTTTCAGATGCCGGCCCCACG
GCCTAT

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FIG. 6A

HASGQRCVLLRTWEALAPATPAMPRAPRCRAVRSLLRSHYREVLPLATF
VRRLGPQGWRLVQRGDPAAFRALVAQCLVCPWDARPPPAAPSFRQVSC
LKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPN
TVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPP
LYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARR
RGGSASRSLPLPKRPRRGAAPEPERTFVGQGSWAHPGRTRGPSDRGFCV
VSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPC
PPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRP
WMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLRAAV
TPAAGVCAREKPGQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRAC
LRRLVPPGLWGSRHNERFLRNTKKFISLGKHAKLSLQELTWKMSVRDC
AWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTET
TFQKNRLFFYRKS VWSKLQSIGIROHLKRVQLRELSEAEVRQHREARPA
LLTSRLRFIPKPDGLRPVNM DYVVGARTFRREKRAERLTSRVKALFSV
LNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPPELYFVKVDV
TGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSH
VSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLR
FMCHHAVRIRGKSYVQCQGIPOGSILSTLLCSLCYGD MENKLFAGIRRD

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FIG.6B

GLLLRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNF PV

EDEALGGTAFVQMPAHGL

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FIG. 7

TCCCCTGGTGCGGCCTGCTGCTGGATACCCGGACCCTGGAGGTGCAGAGCGACT
ACTCCAGCTATGCCCCGGACCTCCATCAGAGCCAGTCTCACCTTCAACCGCGGCT
TCAAGGCTGGGAGGAACATGCGTCGCAAACTCTTTGGGGTCTTGCGGCTGAAGT
GTCACAGCCTGTTTCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCA
ACATCTACAAGATCCTCCTGCTGCAGGCGTACAGGTTTCACGCATGTGTGCTGC
AGCTCCCATTTTCATCAGCAAGTTTGGAAGAACCCACATTTTTCCTGCGCGTCA
TCTCTGACACGGCCTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGA
TGTCGCTGGGGGCCAAGGGCGCCGCCGGCCCTCTGCCCTCCGAGGCCGTGCAGT
GGCTGTGCCACCAAGCATTCTGCTCAAGCTGACTCGACACCGTGTACCTACG
TGCCACTCCTGGGGTCACTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCC
CGGGGACGACGCTGACTGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAG
ACTTCAAGACCATCCTGGACTGATGGCCACCCGCCCACAGCCAGGCCGAGAGCA
GACACCAGCAGCCCTGTCACGCCGGGCTCTACGTCCCAGGGAGGGAGGGGCGGC
CCACACCCAGGCCCGCACCGCTGGGAGTCTGAGGCCTGAGTGAGTGTTTGCCG
AGGCCTGCATGTCCGGCTGAAGGCTGAGTGTCGGCTGAGGCCTGAGCGAGTGT
CCAGCCAAGGGCTGAGTGTCAGCACACCTGCCGTCTTCACTTCCCCACAGGCT
GGCGCTCGGCTCCACCCAGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTCCA
CTCCCCACATAGGAATAGTCCATCCCCTGAT

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FIG.8A

CCACGCGTCCGGGCAGCGCTGCGTCCTGCTGCGCACGTGGGAAGCCCTGGCCCC
GGCCACCCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCGTGCGCTCCCTGCT
GCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTTCGTGCGGCGCCTGGG
GCCCCAGGGCTGGCGGCTGGTGCAGCGCGGGGACCCGGCGGGCTTTCCGCGCGCT
GGTGGCCCAGTGCCCTGGTGTGCGTGCCCTGGGACGCACGGCCGCCCCCGCCGC
CCCCCTCCTTCCGCCAGGTGTCCTGCCTGAAGGAGCTGGTGGCCCGAGTGCTGCA
GAGGCTGTGCGAGCGCGGCGCGAAGAACGTGCTGGCCTTCGGCTTCGCGCTGCT
GGACGGGGCCCGCGGGGGCCCCCCCCGAGGCCTTCACCACCAGCGTGCGCAGCTA
CCTGCCCAACACGGTGACCGACGCACTGCGGGGGAGCGGGGCGTGGGGGCTGCT
GCTGCGCCGCGTGGGEGACGACGTGCTGGTTCACCTGCTGGCACGCTGCGCGCT
CTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCGCTGTA
CCAGCTCGGCGCTGCCACTCAGGCCCCGGCCCCCGCCACACGCTAGTGGAACCCG
AAGGCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGTCAGGGAGGCCGGGGT
CCCCCTGGGCCTGCCAGCCCCGGGTGCGAGGAGGCGCGGGGGCAGTGCCAGCCG
AAGTCTGCCGTTGCCCAAGAGGCCAGGCGTGCGCTGCCCCTGAGCCGGAGCG
GACGCCCCGTTGGGCAGGGGTCCTGGGCCCACCCGGGCAGGACGCGTGGAACGAG
TGACCGTGGTTTTCTGTGTGGTGTACCTGCCAGACCCGCCGAAGAAGCCACCTC
TTTGGAGGGTGCGCTCTCTGGCACGCGCCACTCCCACCCATCCGTGGGCCGCCA
GCACCACGCGGGCCCCCATCCACATCGCGGCCACCACGTCCCTGGGACACGCC
TTGTCCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTCAGGCGACAA

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FIG.8B

GGAGCAGCTGCGGCCCTCCTTCCTACTCAGCTCTCTGAGGCCCAGCCTGACTGG
CGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCAGGCCCTGGATGCCAGG
GACTCCCCGCAGGTTGCCCCGCCTGCCCCAGCGCTACTGGCAAATGCGGCCCT
GTTTCTGGAGCTGCTTGGAACACGCGCAGTGCCCCCTACGGGGTGCTCCTCAA
GACGCACTGCCCCGCTGCGAGCTGCGGTACCCCCAGCAGCCGGTGTCTGTGCCCG
GGAGAAGCCCCAGGGCTCTGTGGCGGCCCCCGAGGAGGAGGACACAGACCCCCG
TCGCTTGGTGACAGCTGCTCCGCCAGCACAGCAGCCCCCTGGCAGGTGTACGGCTT
CGTGCGGGCCTGCCTGCGCCGGCTGGTGCCCCCAGGCCTCTGGGGCTCCAGGCA
CAACGAACGCCGCTTCCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCA
TGCCAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCGGGACTGCGC
TTGGCTGCGCAGGAGCCCAGGGGTTGGCTGTGTTCCGGCCGCAGAGCACCGTCT
GCGTGAGGAGATCCTGGCCAAGTTCCTGCACTGGCTGATGAGTGTGTACGTCTGT
CGAGCTGCTCAGGTCTTTCTTTTATGTCACGGAGACCACGTTTCAAAGAAGAG
GCTCTTTTTTCTACCGGAAGAGTGTCTGGAGCAAGTTGCAAAGCATTGGAATCAG
ACAGCACTTGAAGAGGGTGACAGCTGCGGGAGCTGTCGGAAGCAGAGGTCAGGCA
GCATCGGGAAGCCAGGCCCCGCCCTGCTGACGTCCAGACTCCGCTTCATCCCCAA
GCCTGACGGGCTGCGGCCGATTGTGAACATGGACTACGTCTGTGGGAGCCAGAAC
GTTCCGCAGAGAAAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACTGTT
CAGCGTGCTCAACTACGAGCGGGCGCGGCCCGGCCCTCCTGGGCGCCTCTGT
GCTGGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGTGCG

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FIG.8C

GGCCCAGGACCCGCCGCTGAGCTGTACTTTGTCAAGGTGGATGTGACGGGCGC
GTACGACACCATCCCCAGGACAGGCTCACGGAGGTCATCGCCAGCATCATCAA
ACCCCAAGAACACGTACTGCGTGCGTCGGTATGCCGTGGTCCAGAAGGCCGCCCA
TGGGCACGTCCGCAAGGCCTTCAAGAGCCACGTCTCTACCTTGACAGACCTCCA
GCCGTACATGCGACAGTTTCGTGGCTCACCTGCAGGAGACCAGCCCGCTGAGGGA
TGCCGTTCGTTCATCGAGCAGAGCTCCTCCCTGAATGAGGCCAGCAGTGGCCTCTT
CGACGTCTTCCTACGCTTCATGTGCCACCACGCCGTGCGCATCAGGGGCAAGTC
CTACGTCCAGTGCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCTG
CAGCCTGTGCTACGGCGACATGGAGAACAAGCTGTTTGCGGGGATTTCGGCGGGA
CGGGCTGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACCTCAC
CCACGCGAAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGAGTATGGCTG
CGTGGTGAACCTGCGGAAGACAGTGGTGAACCTCCCTGTAGAAGACGAGGCCCT
GGGTGGCACGGCTTTTGTTCAGATGCCGGCCACGGCCTATTCCCCTGGTGCGG
CCTGCTGCTGGATACCCGGACCCTGGAGGTGCAGAGCGACTACTCCAGCTATGC
CCGGACCTCCATCAGAGCCAGTCTCACCTTCAACCGCGGCTTCAAGGCTGGGAG
GAACATGCGTCGCAAACCTCTTTGGGGTCTTGCGGCTGAAGTGTACAGCCTGTT
TCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCAACATCTACAAGAT
CCTCCTGCTGCAGGCGTACAGGTTTACGCATGTGTGCTGCAGCTCCCATTTC
TCAGCAAGTTTGGAAGAACCCACATTTTTCCTGCGCGTCATCTCTGACACGGC
CTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGATGTGCGCTGGGGGC

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FIG.8D

CAAGGGCGCCGCGGCCCTCTGCCCTCCGAGGCCGTGCAGTGGCTGTGCCACCA
AGCATTCCTGCTCAAGCTGACTCGACACCGTGTACCTACGTGCCACTCCTGGG
GTCACTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCCCGGGGACGACGCT
GACTGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAGACTTCAAGACCAT
CCTGGACTGATGGCCACCCGCCCACAGCCAGGCCGAGAGCAGACACCAGCAGCC
CTGTCACGCCGGGCTCTACGTCCCAGGGAGGGAGGGGCGGCCACACCCAGGCC
CGCACCGCTGGGAGTCTGAGGCCTGAGTGAGTGTTTGGCCGAGGCCTGCATGTC
CGGCTGAAGGCTGAGTGTCGGCTGAGGCCTGAGCGAGTGTCCAGCCAAGGGCT
GAGTGTCAGCACACCTGCCGTCTTCACTTCCCCACAGGCTGGCGCTCGGCTCC
ACCCAGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTCCACTCCCCACATAGG
AATAGTCCATCCCCTGAT

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FIG.9A

HASGQRCVLLRTWEALAPATPAMPRAPRCRAVRSLLRSHYREVLPLATF
VRRLGPQGWRLVQRGDPAAFRALVAQCLVCVPWDARPPPAAPSFRQVSC
LKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPN
TVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPP
LYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARR
RGGASASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCV
VSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPC
PPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRP
WMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLRAAV
TPAAGVCAREKPGQSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRAC
LRRLVPPGLWGSRHNERFLRNTKKFISLGKHAKLSLQELTWKMSVRDC
AWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTET
TFQKNRLFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPA
LLTSRLRFIPKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKALFSV
LNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPPELYFVKVDV
TGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSH
VSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLR
FMCHHAVRIRGKSYVQCQGIPOGSILSTLLCSLCYGD MENKLFAGIRRD
GLLLRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFV

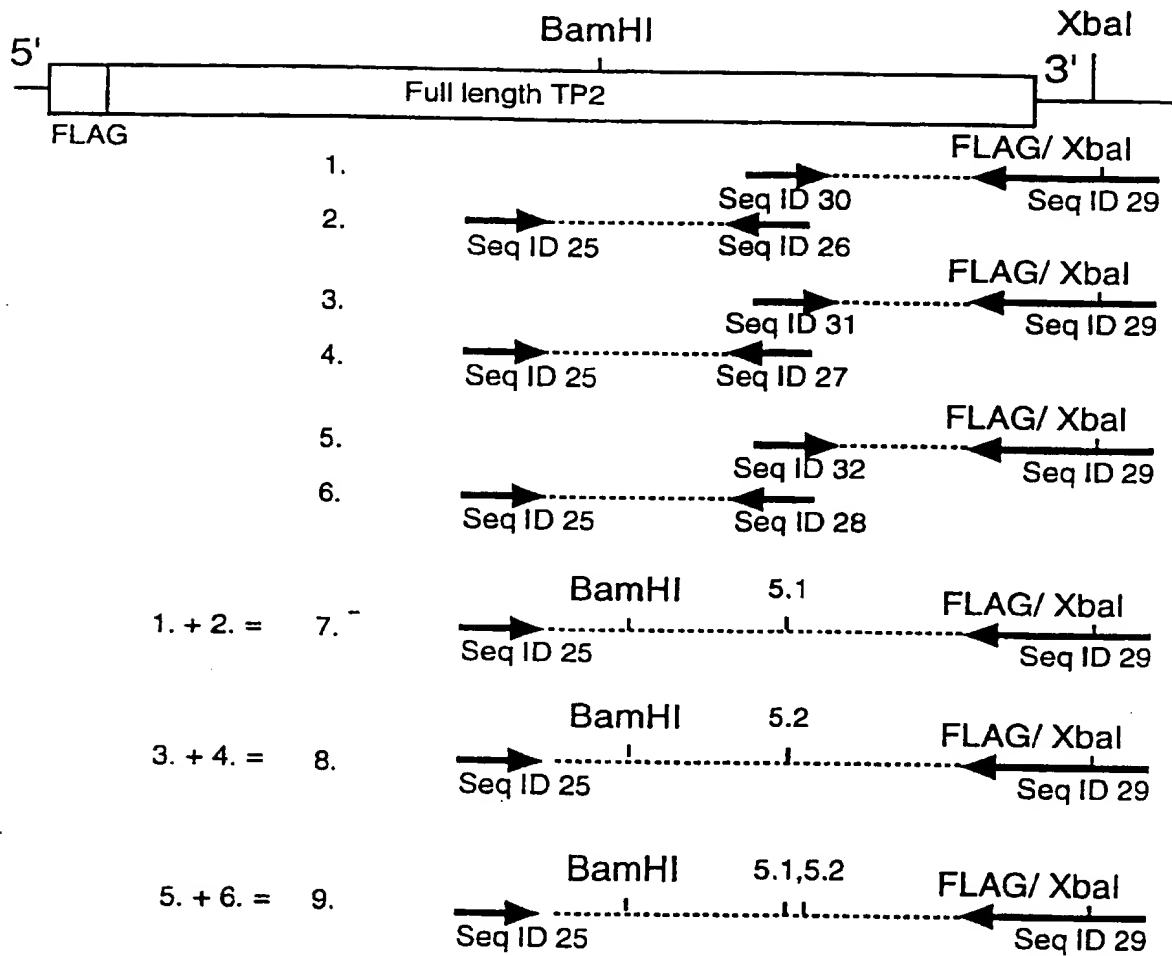
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FIG.9B

EDEALGGTAFVQMPAHGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASL
TFNRGFKAGRNMRRKLFGLRLKCHSLFLDLQVNSLQTVCTNIYKILLL
QAYRFHACVLQLPFHQVWKNPTFFLRVISDTASLCYSILKAKNAGMSL
GAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLRTAQTQLSR
KLPGTTTLTALEAAANPALPSDFKTILD

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FIG. 10



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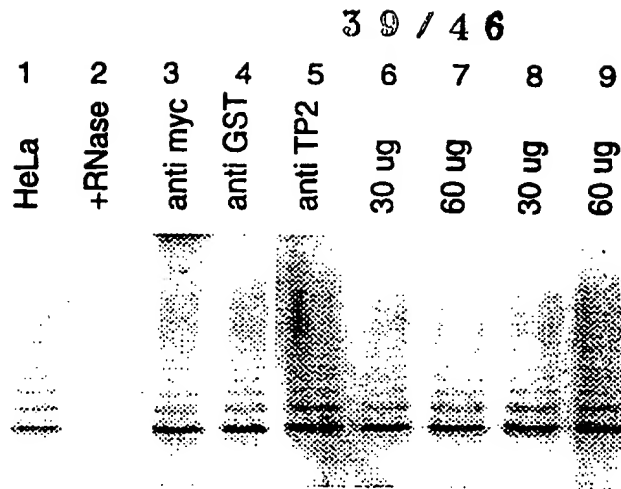


FIG. 11A

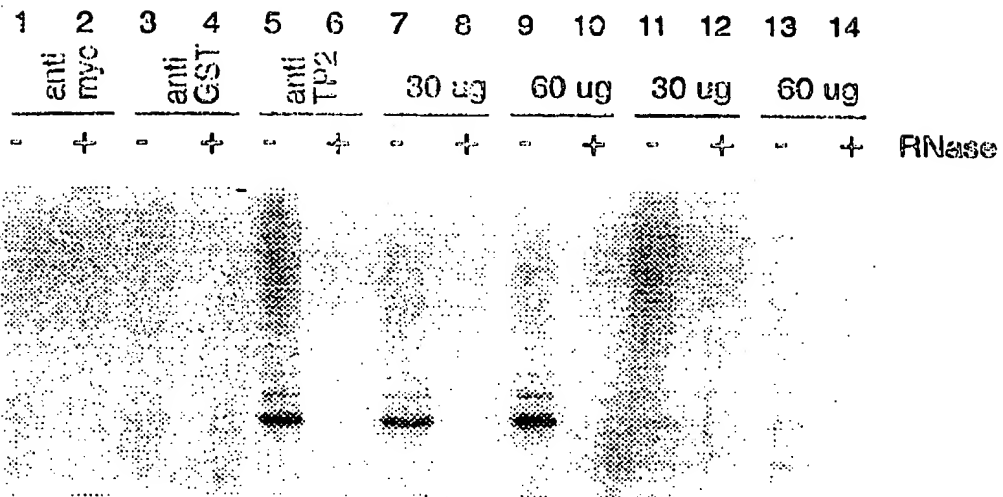


FIG. 11B

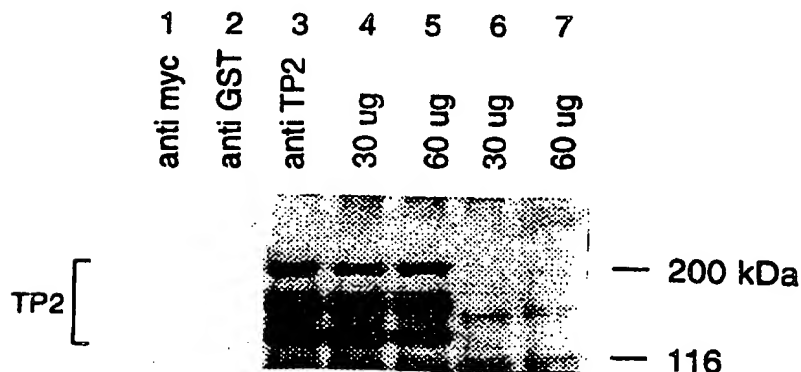


FIG. 11C

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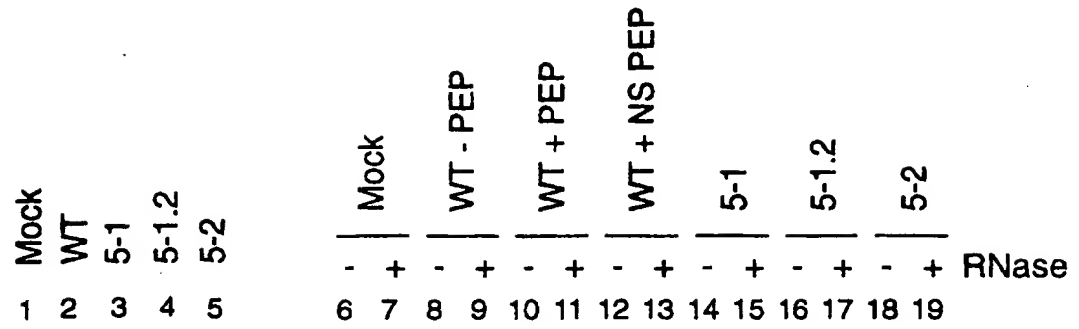


FIG. 12A

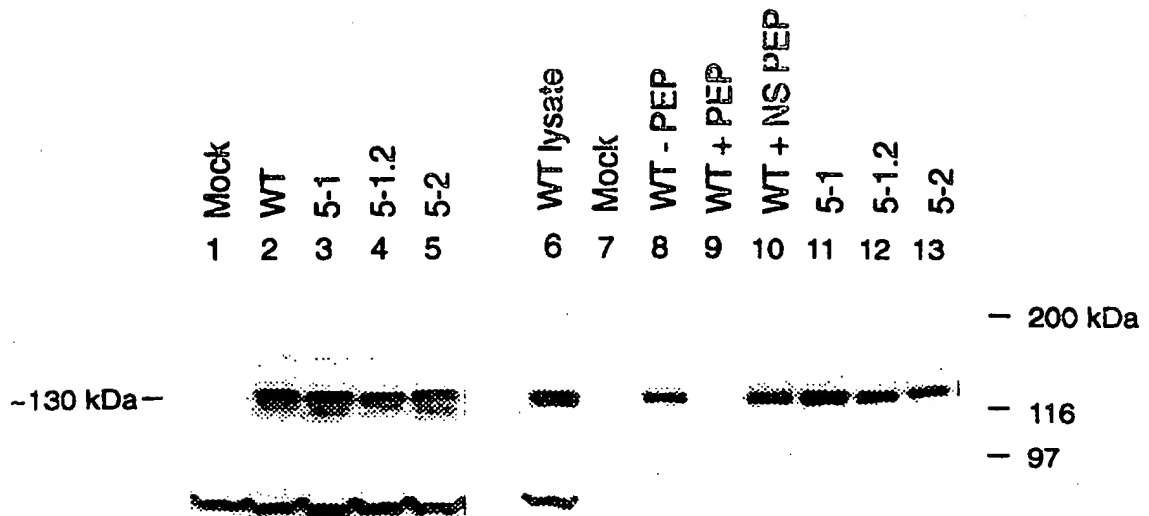


FIG. 12B

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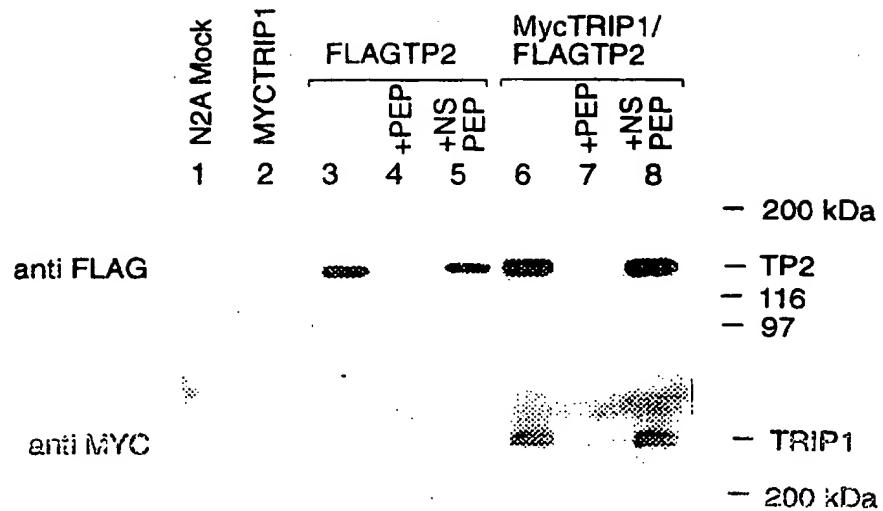


FIG. 13A

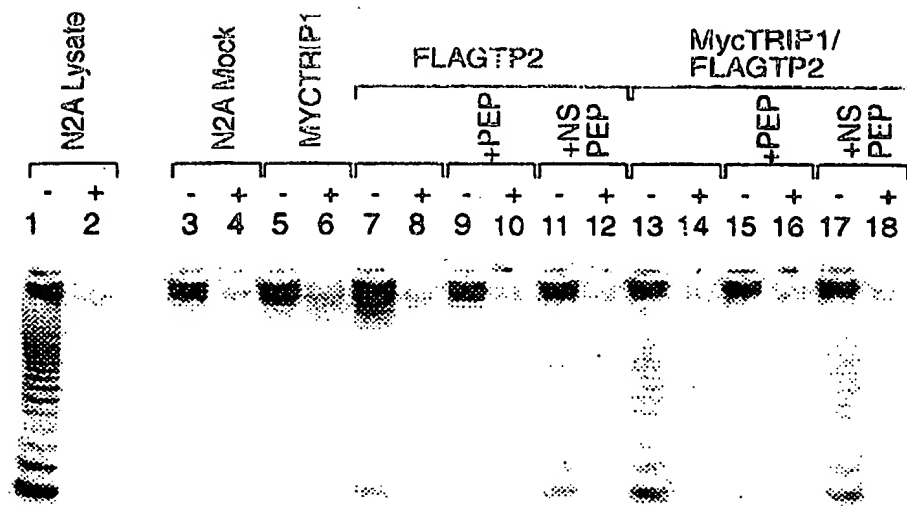


FIG. 13B

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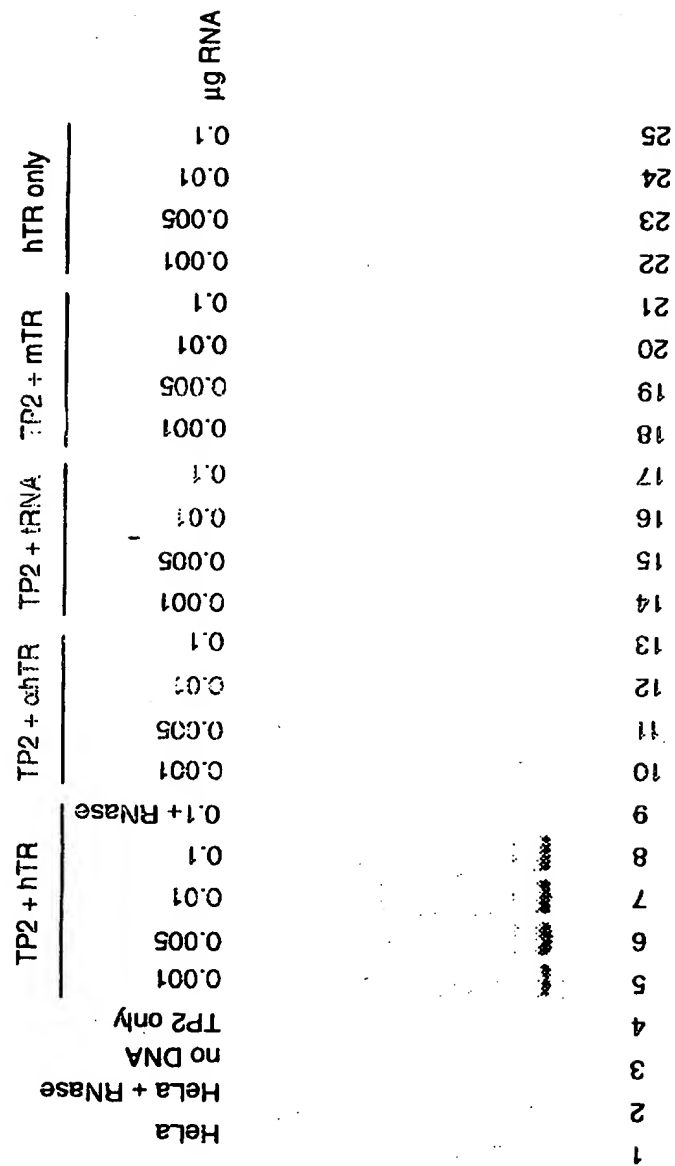


FIG. 14

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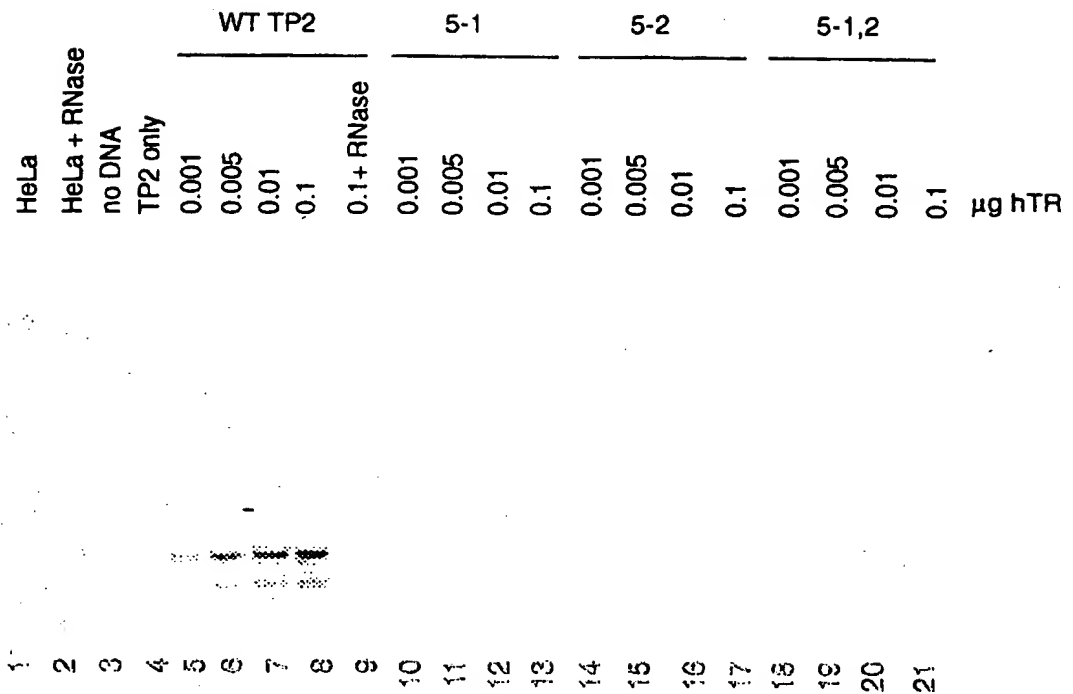


FIG. 15A

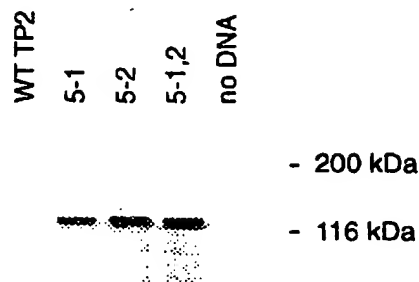


FIG. 15B

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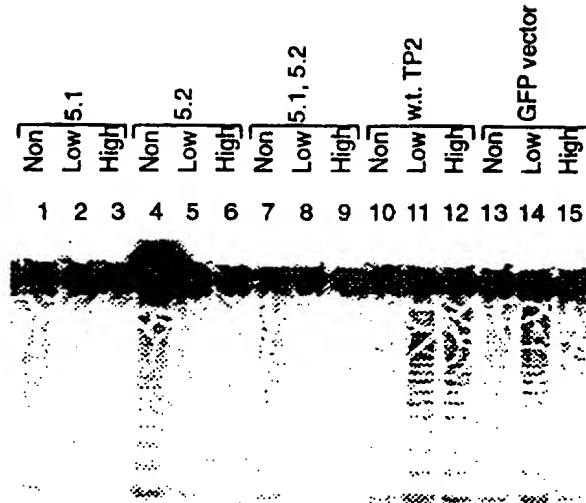


FIG. 16A

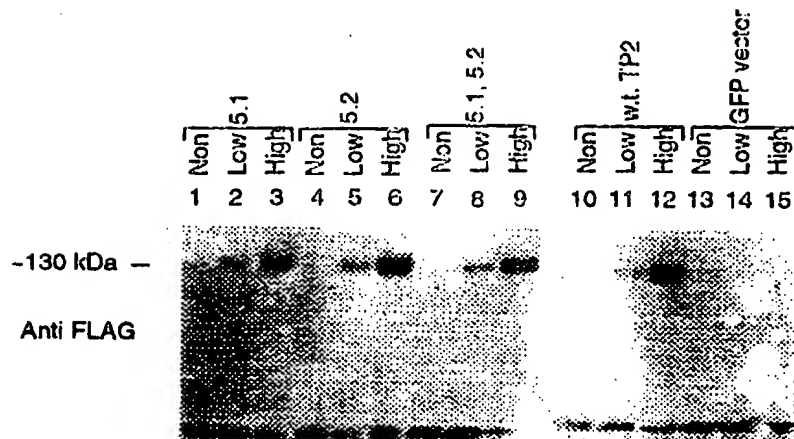


FIG. 16B

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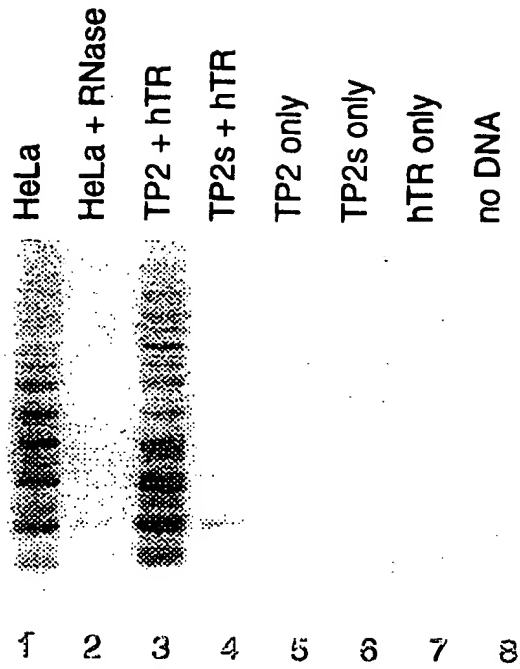


FIG. 17A

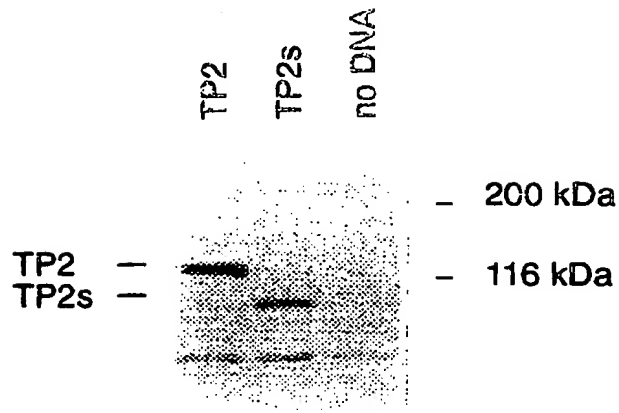


FIG. 17B

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no DNA		TP2+hTR				μ L assayed
		-TP1		+ TP1		
1	2	1	2	1	2	

1 2 3 4 5 6

FIG.18